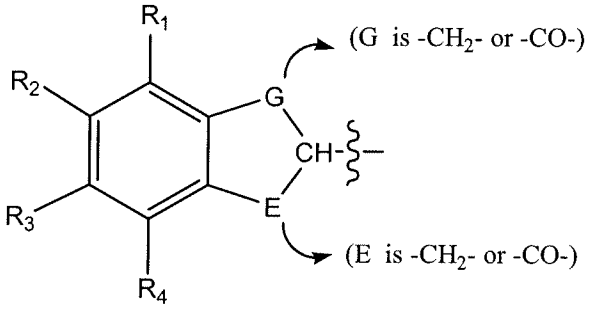
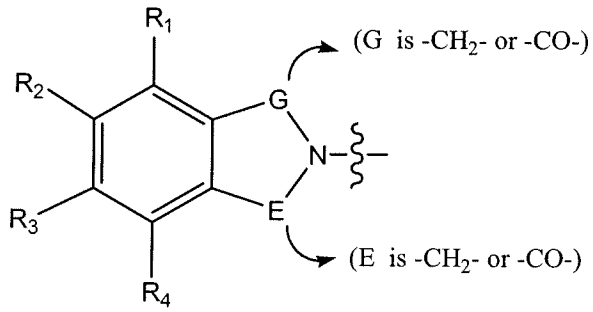
REMARKS

Claims 19-29 are pending. Claims 26-29 presently stand withdrawn as being drawn to non-elected subject matter. Claims 19-25 are presently under examination.

Claim Amendments

Applicants have amended claim 19 to require that D must be selected from -CH-and -N-; and each of E and G must be, independently, -CO- or -CH_2-. As such, claim 19 as presently amended now only encompasses compounds in which X is certain indan-2-yl or 1,3-dihydroisoindol-2-yl rings:





Further, claim 19 as presently amended now requires:

- L must be selected from –C(R)(R′′)-, -CO-, and –NR′-;
- R and R′′ must each be independently selected from hydrogen and alkyl;

- A_1, A_2, A_3, A_4, A_5, A_7, A_8 must each be independently selected from -$C(R_{10})(R_{11})$- and =$C(R_{10})$-;
- R_1, R_2, R_3, and R_4 must each be independently selected from hydrogen and alkoxy; and
- R_{10} and R_{11} are independently selected from hydrogen and halo.

Applicants have amended claim 20 to comport in scope with claim 19 as presently amended.

The foregoing amendments, which introduce no new matter, are being made for the sole purpose of expediting prosecution of the present application; and Applicants expressly reserve the right to pursue any cancelled subject matter in one or more continuing applications.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 19-25 are rejected for allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. The rejection states, in part (Office Action, page 2):

> [T]he specification, while being enabling for the R', R''. R1-R12 to be H, alkoxy or halogen does not reasonably provide enablement for all the various substitutents such as heteroaryl, ... cycloalkyl, or aryls and the numerous functional groups, which may be further substituted.

[1] Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution of the present application, Applicants have amended claim 19 to require *inter alia* the following:

- D must be selected from -CH-and -N-;
- each of E and G must be, independently, -CO- or -CH_2-;
- L must be selected from –C(R)(R′′)-, -CO-, and –NR′-;
- R and R′′ must each be independently selected from hydrogen and alkyl;

- A_1, A_2, A_3, A_4, A_5, A_7, A_8 must each be independently selected from -$C(R_{10})(R_{11})$- and =$C(R_{10})$-;
- R_1, R_2, R_3, and R_4 must each be independently selected from hydrogen and alkoxy; and
- R_{10} and R_{11} must each be independently selected from hydrogen and halo.

[2] One need not disclose every species encompassed by a genus to enable a claim to that genus, even in the unpredictable arts. *See, e.g., In re Angstadt and Griffin* 190 U.S.P.Q. 214, 218 (CCPA, 1976), in which the Court held (emphasis in original) " appellants are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art."

In general, one can rely on the disclosure of representative compounds to satisfy the enablement requirement of § 112, first paragraph for a claimed genus. *See, e.g., Regents of University of California v. Eli Lilly & Co.* 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) (underline emphasis added):

> This is analogous to enablement of a genus under § 112, ¶ 1, **by showing the enablement of a representative number of species within the genus**. See *Angstadt*, 537 F.2d at 502-03, 190 USPQ at 218 (deciding that applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art" and that the disclosure of forty working examples sufficiently described subject matter of claims directed to a generic process); ...

[3] The substituents in the exemplified compounds that correspond to the variables listed above (as well as the other that form part of formula (I)) are representative of the scope of the Markush groups that define each of these variables in claim 19 as presently amended. The specification provides both general and specific procedures for synthesizing the claimed compounds including working examples of the claimed compounds that again are representative in both number and variety of the claimed genus. The skilled artisan, using his or her knowledge of chemistry and the teachings of the specification, could therefore also prepare the non-exemplified members of the claimed genus and do so without undue experimentation. Further,

the specification provides art-recognized assays for evaluating the biological activity, along with evidence showing that representative members of the claimed genus are active in these assays.

It is therefore submitted that the present claims comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

Applicants respectfully request reconsideration and withdrawal of the rejection in view of the foregoing remarks and amendments to claim 19.

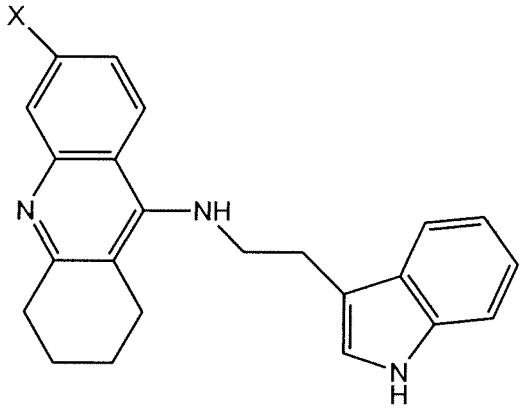
Rejections under 35 U.S.C. § 103

I. Claims 19-25 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over "WO 01/17529 Hu Ming-Kuan" (Office Action, page 7; referred to herein as "Hu"). The Office appears to rely on the disclosure of the compounds **8a-c** (*infra*) in Hu as the basis for the rejection (Office Action at page 7).

Applicants respectfully traverse.

[A] Hu

Hu discloses "a series of rationally designed chloro-substituted bis-tacrines" (Hu, page 3, lines 5-6). There are over 70 compounds disclosed in Hu, and all but three of the compounds disclosed in Hu contain two tacrine residues that are tethered to one another *via* an unsubstituted alkylene chain (referred to herein as "bis-tacrines"). The aforementioned three exceptions have the general formula shown below and are labeled as compounds **8a-c** in Hu (X in the compounds below are H, Cl, or F, respectively):



It is noted that the above-described compounds are same compounds relied upon by the Office in the present rejection. As can be seen, the substituent in compounds **8a-c** that corresponds to Applicants' X is an unsubstituted indole ring.

However, compounds **8a-c** in Hu are only mentioned in connection with the synthesis of different (homodimeric) bis-tacrines. More specifically, Hu only mentions that compounds **8a-c** were prepared "under similar conditions" to those used to make bis-tacrines (Hu, page 4, line 1). Further, Hu does not provide any activity data for compounds **8a-c**. In fact, Hu is devoid of any biological data. As such, there is no way to tell from Hu whether compounds **8a-c** were even found to be active.

[B] The Federal Circuit in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.* 533 F.3d 1353, 1358 (2008) discussed the requirements for establishing whether a claimed compound is *prima facie* obvious over a reference compound (emphasis added):

> The Supreme Court's analysis in *KSR* thus relies on several assumptions about the prior art landscape. First, *KSR* assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. *See Takeda*, 492 F.3d at 1357 ("**Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound**."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S.Ct. at 1742. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed.Cir.2008), this court further explained that this "easily traversed, small and finite number of alternatives ... might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, *KSR's* focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.

In other words, post- *KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.

[C] Applicants respectfully request reconsideration and withdrawal of the rejection for any one of the following two independent reasons discussed in sections **[1]** and **[2]** below.

[1] First, the claims as presently amended no longer encompass compounds in which variable X is an indole ring.

[2] Second, "post- *KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" (*Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.* 533 F.3d, 1358). Applicants submit that the teachings of Hu would not have led one to select any one of compounds **8a-c** in Hu as a lead compound, much less modify any one of these compounds in the manner needed to arrive at the claimed compounds. This is discussed in more detail below.

Hu does not provide any activity data for compounds **8a-c**. In fact, Hu is devoid of any biological data. As such, there is no way to tell from Hu whether compounds **8a-c** were even found to be active. Thus, there is no apparent basis in Hu for selecting compounds **8a-c** as a lead compound for further study.

Further, to arrive at the claimed compounds, one would at least need to modify compounds **8a-c** in Hu in the following manner: (i) replace the indole nitrogen with -CO- or -CH_2-; (ii) replace the indole C-2 (an sp^2 carbon) with -CH- or -N- and then make this ring atom the point of attachment for the remainder of the molecule; and (iii) replace the indole C-3 with -CO- or -CH_2- and then no longer have this position of the ring be the point of attachment for the remainder of the molecule. There is no explicit or implicit disclosure in Hu that would have led a person of ordinary skill in the art to make any one of the foregoing modifications, much less all of them in combination -- the only compounds mentioned in Hu are those in which the substituent corresponding to Applicants' X is a tacrine residue or an unsubstituted indole ring.

Thus, one of ordinary skill in the art would not have been motivated by Hu to prepare the claimed compounds. *See Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350, 1357 (Fed. Cir. 2007): "Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."

In view of the foregoing, Applicants respectfully request that the 35 U.S.C. § 103 rejection over Hu be reconsidered and withdrawn.

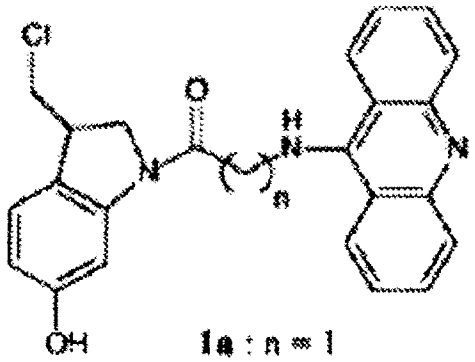
II. Claims 19-25 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over "Fan et al 1997, Synthesis, DNA binding and cytotoxicity of 1-[[ω-(9-acridinyl)amino]alkyl]carbonyl-3-(chloro-methyl)-6-hydroxyindolines, a new class of DNA-targeted alkylating agents" (Office Action, page 8). For purposes of clarification, it is believed that the following citation was intended: Fan et al., *Anti-Cancer Drug Design*, Volume 12, Number 4, **1997**, pp. 277-293(17). The reference is referred to herein as "Fan."

The Office appears to rely on the disclosure of the compounds **1a-c** (*infra*) in Fan as the basis for the rejection (Office Action at page 7).

Applicants respectfully traverse.

[A] Fan

Fan discloses the synthesis of DNA- targeted alkylating agents having the following formulae (referred to throughout as "the Fan compounds"):



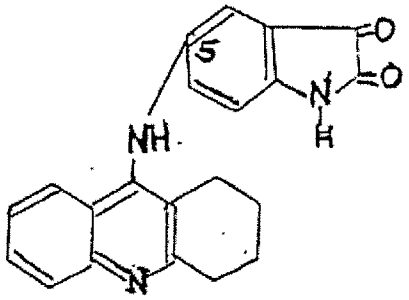
1a : n = 1
1b : n = 3
1c : n = 5

According to Fan (page 277):

> We report the first synthesis of examples of the *seco*-CI DNA alkylating moiety 3-(chloromethyl)-6-hydroxyindoline linked to a 9-aminoacridine DNA-intercalating unit (compounds **1a-1c**).

[B] To arrive at the claimed compounds, one would at least need to replace the chloromethyl group (-CH_2Cl, an **alkylating** moiety) in the Fan compounds with either hydrogen (H) or oxo (=O). This is because the CH-CH_2Cl unit in the Fan compounds corresponds to variables E or G in Applicants' sub-formula X, and claim 19 as presently amended requires that each of E and G must be, independently, -CO- or -CH_2-. However, Fan specifically tells one that the Fan compounds were designed to be DNA- targeted **alkylating** agents. There is no explicit or implicit disclosure in Fan that would have led a person of ordinary skill in the art to replace Fan's chloromethyl group -- an **alkylating** moiety -- with a substituent that lacks this functionality, i.e., hydrogen (H) or oxo (=O). Thus, one of ordinary skill in the art would not have been motivated by Fan to prepare the presently claimed compounds for at least this reason.

III. Claims 19-25 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over "WO 9102725 Nguyen" (Office Action, page 9; referred to herein as "Nguyen"). The Office appears to rely on the disclosure of the following compound in Nguyen as the basis for the rejection (Office Action at page 9, referred to as the "Nguyen compound"):



(VII)

The rejection goes on to state (Office Action, page 10):

> The compounds have the same utility as those of the applicants compounds when 'n' is zero, except that these are positional isomers and the R9 corresponds to and Oxy group, Whereas in applicants compounds it is a hydroxyl group. The compounds are very similar and in the absence of unexpected results are prima-facie obvious.

Applicants respectfully request reconsideration and withdrawal of the rejection for any one of the following two independent reasons discussed in sections **[1]** and **[2]** below.

[1] As can be seen, the substituent in the Nguyen compound that corresponds to Applicants' X is an unsubstituted indoline-2,3-dione ring. The 2-oxo (=O) group of said indoline-2,3-dione ring corresponds to Applicants' variable D. The claims as originally filed **and** the claims as presently amended did not and do not, respectively, encompass compounds in which the substituent corresponding to Applicants' variable D is -CO-. Further, the claims as presently amended no longer encompass compounds in which variables E or G is nitrogen.

[2] According to the Office Action:

> The compounds have the same utility as those of the applicants compounds when 'n' is zero, except that these are positional isomers and the R9 corresponds to and Oxy group, Whereas in applicants compounds it is a hydroxyl group. The compounds are very similar and in the absence of unexpected results are prima-facie obvious.

[a] Obviousness is a legal conclusion based on underlying findings of fact. The obviousness inquiry under 35 U.S.C. § 103(a) is "highly fact-specific by design." *In re Ochiai* 37 USPQ2d 1127, 1131 (Fed. Cir. 1995). "Whether invention exists over prior art isomers and homologues is a question to be decided in each case." *In re Henze* 85 USPQ 261, 264 (CCPA 1950). The Office has cited cases in which a particular chemical modification (positional isomerism) of a known compound was held to be an obvious modification of that known compound. These cited cases, however, do not in and of themselves establish or imply that there exists any *per se* or general obviousness rule that a compound obtained *via* such a modification is obvious over the known compound. As the Federal Circuit explained in *Ochiai*:

> ...the examiner incorrectly drew from *Durden*, a case turning on specific facts, a general obviousness rule: namely, that a process claim is obvious if the prior art references disclose the same general process using similar starting materials.[5] No such per se rule exists. Mere citation of *Durden*, *Albertson*, or any other case as a basis for rejecting process claims that differ from the prior art by their use of different starting materials is improper, as it sidesteps the fact-intensive inquiry mandated by section 103. In other words, there are not '*Durden* obviousness rejections' or '*Albertson* obviousness rejections,' but rather only section 103 obviousness rejections. *Ochiai* at 1131 (italics in original).

[b] Here, the Office merely asserts that the claimed compounds are "positional isomers" of the Nguyen compound, but does not provide any reason why one would have modified the Nguyen compound in the particular manner needed to arrive at the claimed compounds (*see Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350, 1357 (Fed. Cir. 2007)). It is therefore submitted that the Office has not established that the claimed compounds are *prima facie* obvious over Nguyen. This is discussed in more detail below.

[c] Assuming one had reason to modify the Nguyen compound (and Applicants do not concede that this is the case, nor do Applicants concede that the Office has provided any reason why the skilled artisan would have identified and selected the Nguyen compound as a lead compound for further study), then one would have needed to make at least three different particular modifications of the Nguyen compound in order to arrive at the claimed compounds:

> **(i)** replace the nitrogen of the indoline-2,3-dione ring with either hydrogen (H) or oxo (=O) (this is because the NH unit in the Nguyen compound corresponds to variables E or G in Applicants' sub-formula X, and claim 19 as presently amended requires that each of E and G must be, independently, -CO- or -CH_2-): and
>
> **(ii)** replace the 2-oxo group of the indoline-2,3-dione ring with either with -CH- or -N- and then make this ring atom the point of attachment for the 5-amino-1,2,3,4-tetrahydroacridinyl group; and
>
> **(iii)** replace the 5-amino-1,2,3,4-tetrahydroacridinyl group attached to the phenyl portion of the indoline-2,3-dione ring with hydrogen (H) and move the 5-amino-1,2,3,4-tetrahydroacridinyl group to the other side of the molecule.

[d] One could have potentially modified the Nguyen compound in a number of different places and in a number of different ways (again assuming a reason to modify the Nguyen compound existed, which again Applicants do not concede is the case). However, as the Federal Circuit explained in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350, 1357 (Fed. Cir. 2007) (emphasis added):

> Thus, in cases involving new chemical compounds, it remains necessary to **identify some reason that would have led a chemist to modify a known compound in a particular manner** to establish prima facie obviousness of a new claimed compound.

Here, the Office merely asserts that the claimed compounds are "positional isomers" of the Nguyen compound, which even if one agreed with such a characterization, does not in and of itself establish a *prima facie* case of obviousness (*supra*). The Office does not, however, provide

any reason that would have led a chemist to make any one of the three above-described particular modifications (see sub-section **[c]** above), much less all of them in combination. Thus, the Office does not provide any reason that would have led a chemist to modify the Nguyen compound in the manner necessary to arrive at the claimed compounds. It is therefore submitted that the Office has not established that the claimed compounds are *prima facie* obvious over Nguyen. In view of the foregoing, Applicants respectfully request that the 35 U.S.C. § 103 rejection over Nguyen be reconsidered and withdrawn.

Double Patenting

Claims 19-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 16-24 of USSN 10/887,974. Applicants respectfully disagree with the grounds for the rejection; however, to expedite prosecution of the present application, Applicants have amended claim 19 to require that D must be selected from -CH-and -N-; and each of E and G must be, independently, -CO- or -CH_2- (as such, claim 19 as presently amended now only encompasses compounds in which X is certain indan-2-yl or 1,3-dihydroisoindol-2-yl rings). As such, the claims as presently amended in the present application and the claims pending in USSN 10/887,974 do not overlap, and Applicants respectfully request that the rejection be reconsidered and withdrawn for at least this reason.

The three month petition for extension of time fee of $1110 is being paid concurrently with the Electronic Filing System (EFS). Please apply all other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 18043-0003US1.

Respectfully submitted,

Date: March 9, 2010

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